

**A Placebo-Controlled Effectiveness in INPH  
Shunting (PENS) Trial: Proof of Concept  
Adult Hydrocephalus Clinical Research Network  
(AHCRN) Protocol Number 002**

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This protocol is AHCRN Protocol Number 002, and has been approved by Mark Luciano, M.D., Johns Hopkins University, for implementation with PENS investigators. This study is supported by the Hydrocephalus Association as part of its mission to promote a cure for hydrocephalus and improve the lives of those affected by the condition.

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PROTOCOL TITLE:

A Placebo-Controlled Effectiveness in INPH Shunting (PENS) Trial: Proof of Concept

Short Title: PENS Protocol

Lead Investigator:

Mark Luciano, MD

Johns Hopkins University

Protocol Version: 4.0

Version Date: May 8, 2020

*I confirm that I have read this protocol, I understand it, and I will conduct the study according to the protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and will adhere to the Ethical and Regulatory Considerations as stated. I confirm that if I or any of my staff are members of the Institutional Review Board, we will abstain from voting on this protocol, its future renewals, and its future amendments.*

Principal Investigator Name: \_\_\_\_\_

Principal Investigator Signature: \_\_\_\_\_

Date: \_\_\_\_\_

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# 1 Study Summary

## 1.1 Abstract

Although idiopathic normal pressure hydrocephalus (INPH) has been recognized for five decades, barriers still exist in recognition, referral and accurate diagnosis. Hesitance in referring elderly patients for surgical treatment of INPH results from an incomplete understanding of its pathophysiology, controversy over the appropriate diagnostic work up, and a significant concern about the effectiveness and complications of surgical treatment. The approach to screening, diagnosis and treatment of INPH varies throughout the world, though success rates in experienced centers are similar in uncontrolled studies.

The lack of consensus regarding tests predicting outcome of surgery in INPH, and the skepticism of INPH in the neurology and neurosurgery communities reflect the limitations of INPH clinical research to support current INPH practices. INPH clinical research paradigms have not changed for over 20 years. A survey described the uncertainty surrounding the treatment of INPH and the need for a placebo-controlled study. Convincing proof of shunting effectiveness is likely to increase the number of INPH patients getting adequate treatment.<sup>1</sup>

The Placebo-Controlled Effectiveness in INPH Shunting (PENS) trial is a multi-center blinded, randomized, placebo-controlled design investigation of cerebrospinal fluid (CSF) shunt surgery.

## 1.2 Primary Hypothesis

The primary hypothesis of the PENS trial is that treatment of idiopathic normal pressure hydrocephalus (INPH) with an open shunt results in improved gait velocity.

## 1.3 Study Objectives

### 1.3.1 Primary Objective

The primary study objective is the evaluation of CSF shunting in INPH participants through a group comparison of improvement from baseline at four months between active and placebo-controlled groups, using the primary endpoint of gait velocity, to test the primary hypothesis as above.

### 1.3.2 Secondary Objectives

1. Evaluate the clinical improvement of all study participants at eight months of active shunting, using the primary outcome of gait velocity.



2. Evaluate the effect of shunting between active and placebo-controlled groups at four months using secondary clinical outcome measures as listed below.
3. Evaluate the clinical improvement of all study participants at eight months of active shunting using secondary clinical outcome measures.
4. Identify novel CSF biomarkers that differentiate participants with INPH from Alzheimer's disease (AD) participants and other dementias, adjusting the typical cut-offs of traditional AD related biomarkers for altered volume of distribution when CSF is available from clinical testing.
5. Identify specific biomarkers associated with improved medium term (eight month outcomes) response to active shunting, enabling improved selection of participants in future trials.
6. Compare adverse events (AEs) in the active versus placebo-controlled group at four months and at eight months of active shunting.

The secondary clinical outcome measures are improvement in measures of cognition and mood, function, bladder control and frequency of adverse effects:

- Cognition and Mood:
  - Montreal Cognitive Assessment Test (MoCA)
  - Symbol Digit Modalities Test (SDMT)
  - Beck Depression Inventory, 2nd edition (BDI-II)
  - Lawton Activities of Daily Living/Independence in Activities of Daily Living (ADL/IADL)
- Function: Modified Rankin Scale (MRS)
- Bladder Control: Overactive Bladder Questionnaire, short form (OAB-q sf.)
- Adverse Events: Frequency of falls, surgical and non-surgical complications, related and unrelated

## 1.4 Participant Eligibility

### 1.4.1 Inclusion Criteria:

Participants will be eligible for enrollment if they meet all of the following inclusion criteria:

1. Age  $\geq$  60 years; and

2. Diagnosis of INPH based on the Investigator's clinical judgement based on criteria and testing as described in the INPH Guidelines<sup>2</sup>; and
3. Evans Ratio  $\geq 0.30$ ; and
4. One positive supplementary test to include large volume Lumbar Puncture or extended CSF drainage per institutional standards<sup>3</sup>; and
5. History or evidence of gait impairment (such as decreased step height or length, decreased speed, retropulsion as described in the INPH Guidelines<sup>2</sup>) duration  $\geq 6$  months; and
6. Participant has the sensory motor skills, communication skills and understanding to comply with the testing and reporting required in the PENS trial; and
7. Participant is able to give written informed consent, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.

#### 1.4.2 Exclusion Criteria:

Participants will be ineligible for enrollment if any of the following exclusion criteria are met:

1. Unable to walk 10 meters with or without an assistive device; or
2. Baseline fastest gait velocity  $>1$  m/sec and fastest gait velocity improvement is  $\leq 30\%$  with or without an assistive device; or
3. Unable to return to the study center for follow up evaluation and shunt programming; or
4. Participant is not medically cleared for shunt surgery per local standards; or
5. Secondary NPH. (Prior encephalitis, meningitis, subarachnoid hemorrhage, traumatic brain injury (including concussion) within two years or with brain injury or skull fracture on baseline imaging, brain abscess, brain tumor, obstructive hydrocephalus (including acquired aqueductal stenosis and carcinomatous meningitis)); or
6. Prior or existing shunts, endoscopic third ventriculostomy, or any previous surgical intervention for hydrocephalus; or
7. Previous intracranial neurosurgical procedure; or
8. Current treatment with anticoagulation medications or expected to be on anticoagulation medications in future based on clinician evaluation; or

9. Symptomatic cerebral or cerebellar infarction within 6 months from screening (asymptomatic lacunar infarctions are permitted); or
10. Diagnosis of Parkinsonian syndrome that, in the investigator's judgment, will complicate the outcome evaluation; or
11. Diagnosis of schizophrenia or any psychiatric diagnosis (including depression) that in the investigator's judgment will complicate the outcome evaluation (such as neuroleptic treatment for schizophrenia); or
12. Diagnosis of dementia disorder where the investigator considers cognition deficit limits participation in the study; or
13. Conditions impairing gait that are considered to be unrelated to hydrocephalus, such as hemiparesis, spasticity, cerebellar ataxia or musculoskeletal and joint disease, which will interfere with gait assessment or the potential for gait improvement.

## 2 Rationale and Background

### 2.1 Background

INPH is underdiagnosed because of widespread skepticism regarding diagnostic tests and treatment outcomes. Although thousands of shunts are implanted for INPH each year, a significant proportion of neurologists and neurosurgeons do not believe that INPH can be diagnosed accurately. Further, many physicians believe that shunt surgery does not improve patient outcome, or that the risk of complications is far greater than the odds of benefit.

Demonstration of the clinical effectiveness of shunt surgery on INPH in a placebo-controlled trial may change physicians' practice regarding the need to evaluate and treat properly selected patients for INPH. As a result, the number of appropriately treated patients should increase significantly. Appropriate treatment will result in a reduction of unnecessary impairment and disability, a diminished need for health care services (including nursing home) among the elderly INPH population, with associated reduction in long-term health care expenditures,<sup>4</sup> and a significant economic and psychosocial impact on patients and families. Additional advances in treatment will be facilitated by quantitation of true physiological effects, allowing comparison in subsequent studies. Attention may then focus on the identification of subpopulation that can benefit and demonstrate improvement in shunting materials and methods.

INPH clinical research paradigms have not changed for over 20 years. The lack of consensus regarding INPH diagnostic tests among INPH experts, and the skepticism

of INPH in the neurology and neurosurgery communities reflect the limitations of INPH clinical research to support current INPH practices. While studies showing efficacy have been performed by Dutch, European, and Japanese centers,<sup>5–7</sup> these studies were not placebo controlled and were discrepant in diagnostic method and outcome measures that left questions about true effectiveness and patient selection.

## 2.2 Rationale for Current Study

Subjective factors in evaluation of INPH treatment response, along with the strong potential of surgery and an implanted shunt to elicit a placebo response, have made a scientifically convincing demonstration of the true physiological treatment effect of shunting in INPH difficult. Few studies have attempted to evaluate the extent of physiological versus placebo-induced shunt improvement in INPH. These studies have been small and have often used invasive procedures such as ligation around the distal shunt catheter to produce the placebo condition. This has made true blinding difficult and required a minor surgical procedure to remove the ligation and reverse the placebo condition.

Our study would be the first to take advantage of the virtual off setting of a programmable valve system to result in a blinded non-invasive placebo-controlled study, as we first proposed in 2012.<sup>8</sup>

There is a strong scientific and public health imperative to do such an evaluation. A placebo-controlled study is necessary to determine the clinical response to shunt surgery for INPH. Either result of this study will have an important impact on care of the elderly: If shunting is proven effective, it may be offered to a proportion of the much larger group of INPH candidates that have been estimated.<sup>9, 10</sup> Further, a placebo-controlled study allows the evaluation of the placebo vs. physiological effect that will identify objective thresholds that distinguish shunt responders from non-responders. Alternately, if no difference in clinical or physiological response exists between the shunt and placebo groups, then the existence of shunt-responsive INPH may be questioned and would significantly reduce the number of elderly patients undergoing unnecessary diagnostic procedures and surgery.

The most common reason for failure to improve on the diagnostic tests as well as shunt surgery is the prevalence of AD in the aging population. AD is known to cause ventriculomegaly; and gait abnormalities have been described even in prodromal AD, making the distinction from INPH a clinical challenge. Therefore, CSF will be collected to potentially identify biomarkers that improve the clinician's ability to differentiate between these two conditions.

Difficulty in distinguishing INPH from other common age related neurodegenerative disorders that present with similar symptoms like Lewy body dementia and vascular dementia is considered one of the reasons for poor long term shunt responsiveness and is purely based on radiologic assessment and INPH specific diagnostic tests. Moreover, with increasing age, it is not surprising that INPH can coexist with other age related neurodegenerative disorders which over time would be expected to reduce the benefit from shunt surgery even though the shunt optimally treats INPH. The Infinium Neuro Consortium ArrayR is a new neurogenomic tool with expertly-selected content for the interrogation of genomic variants associated with common neurodegenerative diseases. The array includes 180,000 markers focused on characterization of neurodegenerative diseases. The consortium gathered previously identified markers found in known neurodegenerative disease genes including Alzheimers Disease, Parkinsons Disease, Progressive Supranuclear Palsy (PSP)/Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA), Frontotemporal Dementia (FTD), Dementia with Lewy Bodies (DLB), all disorders that are in the differential diagnosis with INPH. Saliva genotyping will be analyzed using saliva samples collected after enrollment to ascertain the prevalence of common neurodegenerative disorders in those selected for the PENS trial to discover if the lack of responsiveness in those who have received shunt treatment for 12 months could be explained by the prevalence of any single nucleotide polymorphisms (SNPs) related to the above neurodegenerative disorders.

## 3 Study Design and Data Collection

### 3.1 Study Design

The primary intervention will be setting the FDA-approved Certas Plus with Siphonguard, programmable CSF shunt valve to active (open shunt group)(setting 4)(110 mm H<sub>2</sub>O) or placebo (closed shunt group)(setting 8)(>400 mm H<sub>2</sub>O) in a 1:1 ratio.

By the time of the primary objective evaluation at four months, the closed shunt group will have zero months of active treatment, and the open shunt group will have four months of active treatment. At four months, shunts for study participants in the closed Shunt group will be adjusted to setting 4. To maintain blinding, all study participants will be adjusted/ mock adjusted to the active setting in a similar fashion. Participants from both groups will not be adjusted before four months of active treatment, unless judged medically necessary by the treating team. Following four months of active treatment, all participants in each group will have shunt adjustments according to clinical standards at each center.

Procedures and data collection in the trial are displayed in Table 1. Initial baseline assessments should be done by an AHCRN trained assessor prior to or at least two weeks post lumbar puncture (LP) or external lumbar drainage (ELD). Please note

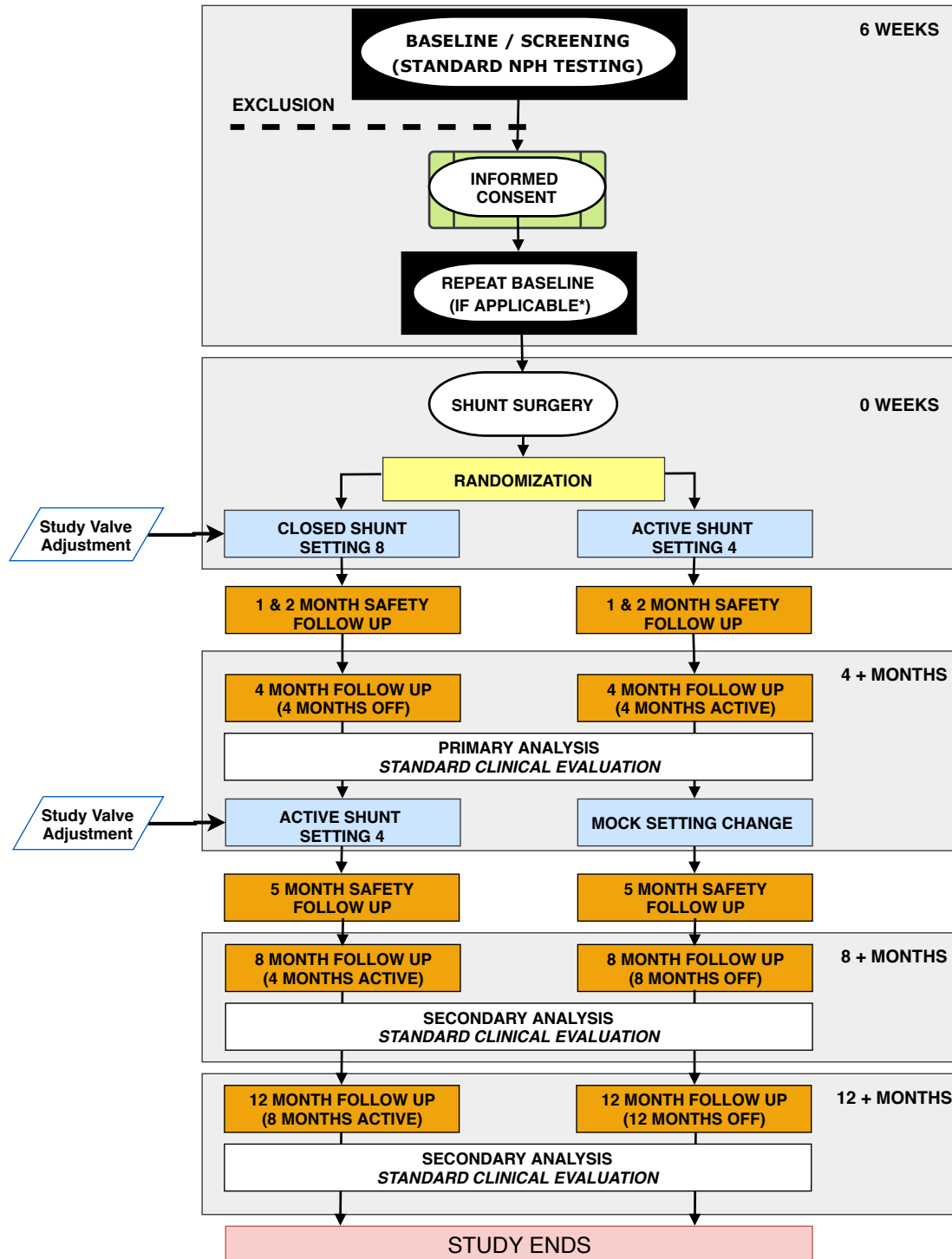


Figure 1: Workflow

that if initial baseline assessments for eligibility are completed by non-AHCRN trained personnel, the gait velocity, MoCA, and SDMT, assessments should be repeated by an AHCRN trained assessor on the day of or after the participant consents and within 6 weeks of the scheduled surgery. If initial baseline assessments are all completed by an AHCRN trained assessor and the surgery is delayed, only the gait assessment should be repeated by the same AHCRN assessor within 6 weeks of the scheduled surgery. Follow-up items listed will have an acceptable window of -14 days to +30 days. Acceptable time between the standard clinical baseline evaluation and surgery is up to six weeks.

Clinical investigators at each site will be neurosurgeons or neurologists. Site staff will screen each clinic patient for potential eligibility. A screening log will be completed for all patients meeting study inclusion criteria, whether eligible or not eligible. After a potential study candidate has been identified at the site, site staff will ask the patient if they would like to hear about the research study. Those who indicate that they are not interested will receive standard treatment. Patients who express interest in participating will be provided with a copy of the informed consent document to review. The site staff will answer any questions or concerns relating to the study. The patient will be informed about the objectives of the study and the potential risks. Patients who choose to participate must sign an informed consent document prior to shunt insertion procedure. Patients who consent to the study will be scheduled for the shunt procedure. Prior to the procedure, site staff will review baseline assessments to make sure they are all completed.

Randomization to open shunt or closed shunt settings will occur at the time of the surgery. Neurosurgeon will perform randomization using an Internet-based randomization system; a block randomization design will be used, with the treatment assignment stratified by site so as to keep participants within a center approximately balanced between groups as the study progresses.

### **3.1.1 Overview of Interventions**

The primary intervention will be the initiation of the randomized initial shunt valve opening pressure setting to create a delayed treatment group in half of the study participants. Randomization will be to active or placebo (closed) shunt settings. At the time of the standard four-month evaluation, all study participants will be similarly non-invasively adjusted to bring all participants in both groups to the active setting while maintaining blinding of the participants. All settings will be verified by the adjusting neurosurgeon.

Item	Screening/ Consenting/ Enrollment	Surgery	One- Month Safety Follow-up	Two- Month Safety Follow-up	Four- Month Follow-up	Five- Month Safety Follow-up	Eight- Month Follow-up	Twelve- Month Follow-up
Screening	X							
CSF Sample (optional)	X							
Consenting	X							
Randomization		X						
Saliva Sample*** (optional)	X							
Surgery		X						
Shunt Programming		X			X			
Pre-OP Imaging	X							
Post-OP CT Scan			X			X		
Gait Velocity Testing	X*/**				X		X	X
MoCA	X**				X		X	X
SDMT	X**				X		X	X
BDI-II	X				X		X	X
Lawton ADL/IADL	X				X		X	X
MRS	X				X		X	X
OAB-q Short Form Symptom Severity Subscale	X				X		X	X
History	X							
Physical Exam	X							
Concomitant Medications	X		X	X	X		X	X
AEs****			X			X		
SAEs*****/Neurological/ Urological AEs*		X	X	X	X	X	X	X

\* If surgery is delayed, assessment should be repeated by same AHCRN trained assessor that performed initial assessment for eligibility. See section 3.2

\*\* Assessment should be repeated by an AHCRN trained assessor if initial assessment was performed by non-AHCRN trained personnel (i.e. Physical Therapy). See section 3.2

\*\*\* Saliva samples will not be collected for participants who have provided blood samples for other hydrocephalus research

\*\*\*\* Adverse events can be reported at the discretion of the clinician

\*\*\*\*\* Serious adverse events

Table 1: Schedule of Assessments



### 3.1.2 Functional Measures

In-clinic standardized assessment of functional measures is strongly preferred in this trial. However, if patients are unable to return for testing due to risks associated with the COVID-19 pandemic, related hospital closures, or unexpected situations limiting access to the clinic or inability to access the blinded assessor, functional measures may be done remotely if it can be arranged with participant and possible family members, suitable app, or video evaluation.

**Gait Velocity:** Gait velocity will be assessed at baseline (prior to randomization) by an AHCRN trained blinded assessor and post-operatively at four, eight and twelve months by the same blinded assessor. While velocity measurement is a standard clinical measurement, we request the following method for uniformity and quality. Study participants will be assessed by an AHCRN trained assessor who is blinded to randomization (for assessments that take place after surgery) under conditions that are standardized and similar at each measurement, e.g., similar footwear to what is usually worn.

Every effort should be made to ensure that each participant is assessed by the same blinded assessor at every follow up clinic visit. Study participants are encouraged to walk in the same manner relative to their status at inclusion and relative to their assistive device, i.e., if a walker or a cane was used in the baseline gait velocity assessment, then the same assistive device (if needed) should be used in the post-operative gait assessment. The test surface should be consistent, i.e., always a hard surface, or always a carpeted surface. Hard surfaces are recommended. The 10-meter distance should be measured and marked on the floor so that the examiner can time properly. The participant is instructed to start walking at the start line and continue to walk as quickly as they feel comfortable, yet safely until they are beyond the finish line.

The examiner starts the clock when the participants leading foot takes its first step and stops the clock when the participants leading foot crosses over the finish line. The time in minutes and seconds (to 1/10th second) are recorded. Three gait velocity tests are performed and recorded. The best (fastest) of all three gait velocity tests will be used to determine eligibility, including percentage of improvement if over 1m/sec, and used for the primary analysis, although the mean will also be evaluated and auxiliary analyses will evaluate these endpoints. Training for uniform assessment of this primary outcome measure will be performed at each center.

**Montreal Cognitive Assessment (MoCA:)** MoCA will be administered at baseline (prior to randomization) by an AHCRN trained blinded assessor and post-operatively by the same blinded assessor at four, eight and twelve months. The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It

assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. Only MoCA version 1 should be used in this trial.

**Symbol Digit Modalities Test (SDMT):** The SDMT provides a measure of sustained attention and processing speed and requires approximately five minutes to perform. SDMT will be administered in a standardized fashion at baseline (prior to randomization) by an AHCRN trained blinded assessor and post-operatively by the same blinded assessor at four, eight and twelve months. Only the standard form should be used in this study.

**Beck Depression Inventory- Second Edition (BDI-II):** The Beck Depression Inventory is a 21-item self-report questionnaire that measures cognitive, affective, somatic, and performance-related symptoms of depression requiring five to ten minutes to perform. Study participants will be asked to complete the inventory at baseline (prior to randomization) and post-operatively at four, eight and twelve months. The test is scored according to the scoring instructions.

**Lawton ADL/IADL Scale:** The Lawton Scale is a 16-item questionnaire used to assess independent living skills requiring five to ten minutes to complete. The ADL/IADL Questionnaire<sup>11</sup> was modified for the Older Americans Resources and Services (OARS) Program developed at the Duke University Center for the Study of Aging and Human Development (2010), and has been published by Psychological Assessment Resources as part of the Calibrated Neuropsychological Normative System.<sup>12</sup> Both self- and informant- ratings are available. For each form, the respondent is asked to rate the examinee's level of everyday functional independence for six physical activities of daily living (ADLs) and nine instrumental activities of daily living (IADLs). The respondent also rates examinee for incontinence. The test is scored according to the scoring instructions. Study participants will be asked to complete the assessment at baseline (prior to randomization) and post-operatively at four, eight and twelve months.

**Modified Rankin Scale (MRS):** The MRS is a six point disability scale with possible scores ranging from zero to five. The examiner completes the scale based on the history and examination of the participant. The test is scored according to the scoring instructions. The scale will be completed at baseline (prior to randomization) by an AHCRN trained blinded assessor and post-operatively by the same blinded assessor at four, eight and twelve months.

**Overactive Bladder-q Short Form (OAB-q) Symptom Severity Subscale:**

The OAB-q SF is a brief, self-administered, participant-reported outcomes tool with two scales assessing symptom bother and health-related quality of life (HR-QOL) in participants with OAB.

This questionnaire asks how much the participant has been bothered by selected bladder symptoms during the past four weeks. The participant is instructed to indicate which answer best describes the extent to which the participant was bothered by each symptom during the past four weeks. The test is scored according to the scoring instructions. Study participants will be asked to complete the form at baseline (prior to randomization) and post-operatively at four, eight and twelve months.

**Cerebrospinal Fluid (CSF) Collection:** If CSF is available or becomes available from clinical testing, the study participant will be asked to give a permission to use the CSF for PENS trial.

**Saliva Collection:** Saliva will be collected after obtaining participant's consent to the study. Results from genotyping will not be reported to the study participants as the testing will not be carried out in a clinical laboratory improvement amendments (CLIA) certified lab. Saliva samples will not be collected for participants who have provided research blood samples for other Hydrocephalus research in the AHCRN network.

### 3.2 Study Data Collection

Clinical data will be collected at the time of enrollment and throughout the intervention period. Follow-up information will be collected at four, eight and twelve months for both groups. This section provides a summary of the data that will be collected.

**Screening, Enrollment and Randomization Period:** Participants will be screened and evaluated for inclusion and exclusion criteria by the clinical investigator with assistance from research coordinator or co-investigator. The clinical investigator must sign off on participant eligibility before participant is randomized. Participants will be asked for permission to enter the trial, and a participant will be enrolled if he or she meets all eligibility criteria and consent is obtained. Demographic information will only be collected from consented participants. Demographic information will include: date of birth, gender, race, and ethnicity. Enrolled participants will then be scheduled for their surgery date where they will be randomized, and receive either an open or closed shunt as previously defined.

**Baseline Period:** Baseline data elements will be collected on all participants who have been enrolled into the study. Information to be collected during this period

include medical and surgical history, physical examination, MRI or CT scan (within six months), gait testing, MoCA, SDMT, BDI-II, ADL/IADL, MRS, and OAB-q sf.

Note: If initial screening gait velocity, MoCA, and SDMT assessments are performed by non-AHCRN trained personnel (e.g. Physical Therapy), these assessments should be repeated by an AHCRN trained assessor within the 6 week window of surgery date. The BDI, ADL/IADL, MRS and OAB-q will not need to be repeated as long as they are completed within the 6 week window of surgery date.

If surgery is delayed and all initial screening assessments were performed by an AHCRN trained assessor, then only the gait velocity test needs to be repeated by the same AHCRN trained assessor that did the initial screening assessments within the six weeks period of the new surgery date.

**Primary Endpoint (Four Months After Shunt Surgery):** Data elements will be collected on all participants who have been enrolled and randomized into the study and return for evaluation. The primary endpoint of gait velocity will be collected at baseline and at four months post surgery to derive velocity change for the primary objective. Velocity will be measured at subsequent follow-up visits for analysis of secondary objectives.

**Secondary Endpoints (Four, Eight and Twelve Months After Shunt Surgery):** Data elements will be collected on all participants who have been enrolled and randomized into the study and return for evaluation. Information to be collected include adverse events, concomitant medications, falls, gait testing, MoCA, SDMT, BDI-II, ADL/IADL, MRS, and OAB-q sf.

**Secondary Safety Endpoints (One, Two, Four, Five, Eight and Twelve Months After Shunt Surgery):**

1. Delayed treatment: increased frequency of falls. Since imbalance is an important clinical risk in INPH, the occurrence of falls will be noted at each follow up visit along with any associated injury or required medical treatment.
2. Programming errors:
  - Lower than intended- risk of overdrainage: headache or subdural hematoma.
  - Higher than intended- risk of decreased shunt effectiveness and delayed improvement.
3. Expected surgical complications: these are the expected adverse events listed in section 10.2.1.

**Participant Withdrawal:** All participants withdrawn early from the study must have a reason for withdrawal recorded on the appropriate data collection form, and the circumstances leading to withdrawal must be described.

- If the study intervention is discontinued by the clinical care team because of adverse events, this does not constitute participant withdrawal from the study. All participants randomized in this study will be analyzed as per the intention-to-treat principle.
- If the participant is determined ineligible after consent but before randomization, the participant will be withdrawn from the study and their medical record will no longer be reviewed for neurological, urological or serious adverse events.

A participant may choose to withdraw from the study at any time and the clinician will determine the most appropriate treatment for the participant. Since participants in the closed group undergo treatment delay, this delay may be terminated by shunt programming to an open state as long as this change is considered medically necessary. The medical course of the participant will continue to be reviewed for neurological, urological or serious adverse events until 12-month post-surgery clinic visit. If the participant experienced such adverse event from the time of surgery to twelve months post operatively, the adverse event will be followed until resolution or 12-month study visit, whichever is earlier.

## 4 Detailed Study Interventions

### 4.1 Shunt Implantation

Surgical shunt implantation is the major procedure taking place in the study. However, since participant selection for surgery and the method of surgery are all part of the surgeon's standard care, it is not considered an intervention of the study. The implanted shunt will be an FDA-approved programmable CSF shunt (Certas Plus with Siphonguard™, Codman, Johnson and Johnson, Raynham, MA USA). The implantation will follow the standard practice and preference of the neurosurgeon.

### 4.2 Blinding

The neurosurgeon performing the implantation surgery will be aware of the assigned setting. A blinded AHCRN trained assessor will perform the gait and cognitive tests during the follow-up visits and will remain blinded to the treatment assignment throughout the course of the study. Other support staff will enter data for the trial.

The neurosurgeon performing the surgery will pre-set the adjustable valves to one of the two designated settings, while the shunt is in the sterile packaging, outside of the operating room, just before the operative case. The setting 4 or 8 will be determined by the randomization that the neurosurgeon will access directly. The setting will be performed and verified by the neurosurgeon alone, without assistance.

The setting will be recorded as “PENS study assigned setting” in the medical record. This variation from standard practice is necessary to preserve blinding of participants and other investigators. If it is necessary for clinical reasons outside the research protocol (and at any institution) to determine the shunt setting, the standard shunt indicator tool can be used to assess the valve setting at any time. Follow up per protocol schedule will continue for those participants whose shunt setting is modified.

### 4.3 Unblinding

As noted in Section 4, the neurosurgeon performing the surgery will be unblinded to the study participant treatment group and will not play a role in administering the study outcome assessments. The neurosurgeon or other medical personnel will assess the assigned/current valve setting using an indicator tool if this is deemed medically necessary to allow potential valve adjustment. Medical necessity is defined as clinician concern for participant risk for injury due to over- (subdural hematoma development) or under- (acute progressive hydrocephalus) drainage. The study participant will continue to receive standard appropriate medical treatment and remain in the study for data collection.

### 4.4 One-Month Post-Surgery Remote Visit

At one month post-surgery ( $-14/+30$  days), participants will be contacted by phone or seen in the clinic and asked about any adverse events that participants have experienced since surgery and their current list of concomitant medications.

### 4.5 Two-Month Post-Surgery Remote Visit

At two months post-surgery ( $-14/+30$  days), participants will be contacted by phone or seen in the clinic and asked about any neurological, urological or serious adverse events that participants have experienced since their one-month follow up phone call and their current list of concomitant medications.

## 4.6 Four-Month Post-Surgery Visit: Primary Objective Measurements and Shunt Setting Change

At the four-month time point ( $-14/+30$  days), the following will be performed: gait velocity, MoCA, SDMT, BDI-II, Lawton ADL/IADL Scale, MRS, OAB-q, assessment of adverse events, verification of concomitant medications and shunt programming using the Certas Plus Indicator Tool in both groups.

For study participants assigned to the closed shunt group (setting 8), the shunt will be set to setting 4 and left at that setting for four months. For participants assigned to the open shunt group (setting 4), the shunt will be set at the discretion of the treating physician according to each center's standards. In this way both groups will receive four months of drainage at the same setting (setting 4) and thereafter be allowed to have adjustments for further optimization.

## 4.7 Post-Surgery Imaging

As part of the standard of care, a CT scan will be done at approximately one month after shunt implantation. A second CT scan will be done at approximately one month after shunt programming (five months post-surgery).

## 4.8 Five-Month Post-Surgery Remote Visit

At five months post-surgery ( $-14/+30$  days), participants will be contacted by phone or seen in the clinic and asked about any neurological, urological or serious adverse events that participants have experienced since their four-month follow up phone call and their current list of concomitant medications.

## 4.9 Eight-Month Post-Surgery Visit

At the eight-month time point ( $-14/+30$  days), the open group will have experienced eight months of active shunting with the first four months restricted to setting 4 and the subsequent four months allowing for the possibility of adjustment as clinically indicated by the neurosurgeon. The closed group will have experienced only four months of active shunting at setting 4. After this time the closed group will be followed for an additional four months of active shunting allowing for discretionary changes by the neurosurgeon before final assessment. The setting of all shunts will be reconfirmed at the eight month post-op visit.

## 4.10 Twelve-Month Post-Surgery Visit

Following completion of all study evaluations for the secondary endpoint analysis at eight months of active shunting for the closed shunt group, the unblinded neuro-



surgeon will confirm the shunt setting with the Certas Indicator Tool. Participant's participation in the study will be complete at this time. The cohort assignment will be revealed to the participant at this 12-month visit ( $-14/+30$  days).

#### 4.11 Other Therapy Guidelines

Standard therapies and medications should be administered according to standard post-operative care at the local site. This includes use of psychoactive medications, occupational and physical therapy, etc. If a study participant must be treated with oral or intravenous anti-coagulation medications, the clinician will use clinical judgement about shunt adjustment following local SOC.

## 5 Data Analysis

### 5.1 General Analytic Issues

All analyses will be undertaken by the intention-to-treat (ITT) principle, wherein all participants randomly assigned to a treatment arm will be counted in that arm regardless of adherence to protocol or possible crossover to the other treatment arm except for adverse events, which will use the as-treated principle (compare the participants based on the treatment regimen that they received).

Therefore, this clinical trial will assess whether open (early treatment) group versus closed (delayed treatment) group leads to an increase in gait velocity from baseline in the open group, and a significantly higher increase in gait velocity than the closed group at four months after shunt surgery. The alpha level for the trial is 0.05. All tests of significance comparing treatment arms will be two-sided.

Secondary analyses of efficacy (which will be clearly noted as non-primary in all publications), as well as safety analyses presented to the Data Safety Monitoring Board (DSMB), will compare study participants according to the treatment actually received. Adherence to the assigned treatment is expected to be high, in the range of 85-90%, based on experience in previous interventional studies.

Participants who drop out or inadvertently crossover will be followed and included in the ITT analysis. Baseline characteristics will be analyzed to determine if there is a need to adjust for differences between groups in exploratory analyses. Sensitivity analyses will be performed to assess the possibility and consequences of non-random loss to follow-up. The proportions of participants experiencing an unscheduled health care visit or any potential adverse effect, as reported by the caregivers, will be compared between groups using the Mantel-Haenszel test, stratified by site.



## 5.2 Primary Analysis: Is Shunting Effective?

Group comparison of closed shunt versus open shunt groups at four months. The primary analysis will compare change in gait velocity from baseline to four months after surgery between the closed and opened groups. An analysis of covariance approach will be used to maximize statistical power. Specifically, a linear regression model will be fit with four-month gait velocity as the outcome, and assigned treatment arm as a binary predictor along with continuous baseline gait velocity. Significance and magnitude of treatment effect will be assessed via the estimated coefficient of treatment in the model and its standard error. For purposes of assessing a significant treatment effect, the primary outcome of gait velocity will be compared between the assigned treatment arm using a two-sided test with a Type I error of 0.05.

## 5.3 Secondary Analyses of Gait Velocity Change

1. Delay effect: group comparison of change after four and eight months of active shunting. A secondary analysis will compare the change in gait velocity after four and eight months of active shunting in the open group versus active shunting in the closed group, to assess whether the delay in opening the shunt may have an effect on improvement in gait velocity.
2. Overall shunting effect: combined-group active shunting effect: gait velocity change will also be assessed in all participants after four and eight months of active shunting; treatment arms may be combined in this latter analysis if there is no evidence of a difference in effects (see above).

These secondary gait velocity analyses, which will be performed using intention-to-treat as well as treatment received, will implement a linear mixed model using all available data from participants in the trial, and a time-varying indicator of treatment (open or closed) as a predictor along with study time point. Appropriate coefficient estimates and standard errors from this model will be used to quantify and compare treatment effects of interest.

## 5.4 Secondary Analysis and Secondary Endpoint Analysis

The secondary efficacy outcomes of the trial will parallel the three analyses described for the primary endpoint of gait velocity change but will involve the secondary endpoints.

These will include the cognitive endpoint of change in MoCA from baseline to four months, and the neuropsychological endpoints of SDMT, BDI-II and ADL/IADL from baseline to four months in a group comparison. Each of these three endpoints will be analyzed using a Type I error of 0.05/3 to determine formal significance, using

analysis of covariance as for the primary outcome analysis. In addition to the formal primary and secondary outcomes analyses, other instruments collected in this trial (MRS, and OAB-q sf) will be analyzed as exploratory outcomes, and all non-primary outcomes will be examined for evidence of effects at four months and eight months after shunting, using approaches analogous to those described above. While formal correction for multiple comparisons will not be performed, publications will clearly identify these analyses as exploratory.

## 5.5 Secondary Analysis: Safety

Safety outcomes of this study will include rates of specific adverse events listed in Safety endpoints. Safety data will be reported to the DSMB by treatment each participant received, with chi-squared tests (exact with mid-p-value, due to small sample sizes) used to compare rates of outcomes between independent study groups. In any safety reporting settings where the same study participant is in both the open and closed groups, this will be noted in the reports and appropriate statistical approaches such as stratification or conditioning will be used to adjust comparisons as appropriate and feasible.

Overall rates of AEs and SAEs will also be reported by treatment received. In addition to the customary presentation of AEs as serious/not serious and related/unrelated, AEs will also be reported according to surgical/nonsurgical.

## 5.6 Power Analysis for Primary Outcome

Pilot data on change in gait velocity, from 96 participants in a multisite NPH database (NPH centers at Cleveland Clinic, Sinai Hospital and Umea University) with baseline gait velocities of 1.0 m/s or less, had a standard deviation of 0.31 m/s for the post-treatment gait velocity, with a Pearson correlation of 0.44 between baseline and follow-up gait velocity. Using these estimates in appropriate, conservative sample size calculations,<sup>13</sup> the proposed analysis of covariance approach for the primary analysis requires the following number of participants completing the study for adequate power, using a two-sided testing approach with 0.05 Type I error:

Therefore, a target sample size of 34 participants, 17 per study arm, will yield 80% power to detect a significant treatment effect if the true benefit of early start versus delayed start on gait velocity at four months is at least 0.275 m/s, and over 85% power if the true benefit is at least 0.3 m/s. The study will plan on enrolling 40 participants to account for possible attrition to no less than 34.

**Interim Analyses and Stopping Rules** This small clinical trial will have limited power to detect a treatment effect if its true magnitude is less than the assumptions of the above Section; in the absence of statistical significance, estimates of effect for

Assumed Four- Month Mean Velocity Change: Closed Arm	Assumed Four- Month Mean Velocity Change: Open Arm	Total Number Required for 80% Power	Total Number Required for 85%	Total Number Required for 90% Power
0.05	0.3	40	46	54
0.05	0.325	34	38	46
0.05	0.35	30	32	38
0.05	0.375	26	28	32

Table 2: Power Analysis for Primary Outcome

primary as well as secondary outcomes will be used to design subsequent trials. As the largest possible sample size is optimal for this setting, the DSMB will be asked to evaluate interim safety outcomes only for the determination of whether the study is to continue. Interim review of efficacy data will not be performed.

## 6 Study Organization

### 6.1 Participating Institutions

This study will be conducted at approximately six sites in the United States, Canada and Europe. Several sites are participating in the Adult Hydrocephalus Research Network (AHCRN) and have already contributed data to the AHCRN Registry. Other institutions may be added as needed to achieve target enrollment, in the case of center attrition or low accrual rate. The University of Utah will serve as the Data Coordinating Center (DCC) which will provide support for protocol adherence, EDC data management, and for-cause monitoring. The Johns Hopkins University Brain Injury Outcomes Coordinating Center will be acting as the Clinical Coordinating Center (CCC) which will provide support for study start-up, contracts, training, and regulatory documentation, and eBinder management. The total duration of the study is three years and nine months: three months for start-up, two years for participant recruitment, one year for follow up completion, and six months for data analysis and submission of manuscript for publication. Target recruitment is 40 participants to allow for attrition to 34 completed participants in one year, or approximately six to nine participants per participating site. It is anticipated that participating sites will each recruit between five and nine participants over one year. Each Center evaluates between 50 and 100 participants annually for INPH and performs shunt surgery in approximately 50% of participants evaluated. Thus, with five centers in the study,

approximately 250 participants per year receive shunt surgery and will be potentially eligible for the study. Accrual of the target sample size of 40 participants would require just over 15% of all eligible participants to agree to study participation and an attrition rate of 15%.

The proposed study is a multi-center blinded, randomized, placebo-controlled investigation of CSF shunt surgery for participants who are considered candidates for CSF shunting for INPH based on the 2005 NPH guidelines.<sup>3</sup>

## 7 Data Management

### 7.1 Clinical Site Data Management

Study data may be recorded on paper forms, or directly entered into the electronic data capture (EDC) system. Paper forms will be retained at the clinical center and data will be entered by clinical site staff into the EDC system provided by the DCC at the University of Utah School of Medicine. The investigator at each participating site is responsible for all aspects of study implementation, including participants follow-up, collection of accurate study data, and correct entry of the data into the data collection system. These tasks may be specifically delegated to other individuals at the site, but the site investigator is responsible to supervise all aspects of the study, and is responsible to assure that all staff involved in this study are adequately trained to perform the delegated tasks.

### 7.2 Electronic Data Capture System: OpenClinica

The DCC uses an open source clinical trial data management system called OpenClinica. OpenClinica is an open source electronic data capture (EDC) system developed by OpenClinica, LLC. OpenClinica is backed by an open source community comprising over 18,000 registered individuals from hundreds of leading industry, academic, and government research institutions in over 100 countries around the world. The DCC at the University of Utah is using this application to support clinical research studies that are conducted within the Adult Hydrocephalus Clinical Research Network (AHCN).

### 7.3 Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Site monitoring is critical to this process. Site monitoring has been a very effective tool for maintaining data quality in previous studies, and we will utilize this process to ensure excellent quality data in the proposed study. Our site monitoring plan is designed to identify problems with sites and methods for handling problems that arise. Site monitors must be provided with full access to study materials and the medical

records for study participants. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the site monitor's review of data in the electronic medical record.

### **7.3.1 Site Monitoring Plan**

A supplemental study-specific monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan will include the number of planned site visits, criteria for focused visits, or additional visits, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g. sample of all study participants within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found. Remote site monitoring schedules will be determined by the CCC or DCC in coordination with the study principal investigator.

### **7.3.2 Clinical Site Monitoring**

Site monitoring visits, when necessary, will be performed by a trained site monitor during the study period to ensure regulatory compliance, participant safety, and to monitor the quality of data collected. Source documents, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. The site initiation may take place in person or remotely as group training made up of site investigators and research coordinators.

### **7.3.3 Remote Monitoring**

Remote monitoring is essential for this study. Remote monitoring involves detailed review of the data entered by the site and consultations with the site investigator and/or research coordinator to review safety and data quality. This may require uploading de-identified copies of specific parts of the medical record, regulatory documentation, or other source documents. Those materials will be compared against the data recorded in the electronic data capture system. This helps assure protocol compliance and accurate data collection. More remote monitoring activities may be conducted early in the trial to assure protocol compliance and identify any training issues that may exist. Documentation will be retained in accordance with Federal requirements. Safety of participants will be monitored and ensured in accordance with the DSMB plan.

## 7.4 Data Coordinating Center (DCC)

The DCC is located in Salt Lake City, Utah, and is based at the University of Utah School of Medicine. The DCC personnel include data analysts, programmers, biostatisticians, project managers and other staff that assist in the overall planning, design, and implementation of the study projects. Services provided include data management, data storage, quality assurance, and monitoring.

### 7.4.1 Data Center Description

The Data Coordinating Center (DCC) in the Department of Pediatrics at the University of Utah School of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the-art, energy efficient data center completed in 2013. The data center facility supports more than 1200 users around the world and provides a secure, reliable, enterprise-wide infrastructure for delivering critical DCC systems and services. The new data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by Rittal's LCP inline cooling technology, providing efficiency, redundancy and modularity. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains a redundant Mitsubishi uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system, early warning smoke detectors and a heat detection warning system to act as a secondary system to the smoke detectors. Security guards are on-site conducting access control and rounds 24/7/365. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

In 2011 the data center began a large scale VMware server virtualization deployment. Currently, the data center has virtualized about 95% of its environment. The virtual environment consists of more than 160 virtual servers and nearly 20 physical servers. The data center's virtualization solution provides key advantages:

- high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process.
- flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time.
- rapid deployment – servers can be provisioned on-demand with minimal waiting on hardware or software.

The data center also enhanced its storage resources by implementing a networked storage system to support its virtualized environment. The data center currently manages over 50 terabytes of data. The storage solution consists of Dell's EqualLogic

PS Series Storage system for providing a virtualized storage area network (SAN). Some of the benefits that are realized through this technology are:

- storage architecture is no longer a bottleneck for IT services;
- performance is better than with the previous architecture;
- tiered storage is now possible;
- provisioning and reclamation of SAN disk will be much easier; and most important,
- the new architecture includes a redesign of the SAN fabric to include complete redundancy.

Production servers running critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. DCC storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly Monday through Friday from 6 am to 6 pm. Incremental backups also are performed each night with full system backups occurring every Friday. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken off site on a weekly basis to an off-site commercial storage facility.

In the event of catastrophic failure, such as a fire in the server facility, daily backups would probably survive because of the fire suppression system and fireproof safe, but there would be obvious delay in re-establishing data center function because the servers will not survive such a disaster. Total destruction of the data center facility could cause the loss of up to one week's data. In future investments, the data center is making co-location, disaster recovery and business continuity solutions a top priority.

DCC information systems are available 24 hours a day, 7 days a week to all users unless a scheduled maintenance interruption is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over. Critical systems availability has exceeded 99.9% for the past two years, and there has been no unscheduled downtime in over five years.

#### **7.4.2 Security and Confidentiality**

The data center coordinates the network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted with virtual



point-to-point sessions using transport security layer (TLS) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption. All of our Web-based systems use the TLS protocol to transmit data securely over the Internet. Direct access to data center machines is only available while physically located inside our offices, or via a VPN client.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff is notified of intrusion alerts. Security is maintained with Windows 2008 user/group domain-level security. Users are required to change their passwords every 90 days, and workstations time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC or in the Department of Pediatrics are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. Highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

## 7.5 Record Access

The medical record and study files (including informed consent) must be made available to authorized representatives of the CCC and DCC, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the Food and Drug Administration (FDA), National Institute of Health (NIH), other Federal funders, and the IRB for each study site.

## 8 Devices

There are 5 major manufacturers of shunts. Until now the valves were either differential pressure valves or flow-regulated valves and none of them had the ability to be turned off even if clinically indicated. Thus doing a placebo study of shunts often involved tying a ligature in the shunt catheter with variable results and adding complexity and



additional intervention to untie the ligature. With the release of the new Codman Certas Plus 2.0, a “virtual off” setting is now available to stop flow of CSF through the shunt system unless intracranial pressures exceed 400 mm which has not been documented in participants with INPH. This shunt would also rapidly enable lowering settings if indicated in the judgement of the treating physician in the placebo arm without necessitating invasive intervention. No other commercially available shunt appropriate for treating NPH offers these features.

## 9 Protection of Human Subjects

### 9.1 Central Institutional Review Board (CIRB)/ Research Ethics Board (REB) Approval

For this trial, A central IRB model will be adopted. Johns Hopkins IRB will serve as the central IRB for the national participating sites. In addition to the CIRB approval, each clinical center must inform their local IRB to fulfill any additional local regulatory requirements. International sites, however, must obtain approval from their respective IRB/REB prior to participating in the study. The designated regulatory staff at Johns Hopkins will track IRB/REB approval status at the international participating centers and will not permit participant enrollment without documentation of initial IRB/REB approval and maintenance of that approval throughout subsequent years of the project.

### 9.2 Informed Consent

This protocol requires that participants sign a consent form. The participant will be informed about the objectives of the study and the potential risks. Participants with INPH will be approached to provide permission to participation in the study. Informed consent will be obtained prior to initiation of study activities. Documentation of informed consent will be maintained at the study site.

### 9.3 Risks

**Medical risks:** Participants are selected for shunt surgery because the clinical assessment of risks and benefits has been found to be favorable. Therefore, participation in the trial is expected to carry the same risk/benefit profile as shunt surgery.

Complications of shunting in this study are expected to be similar to shunt surgery in

standard surgical practice. Based on the European Multicenter Study,<sup>6</sup> the expected complications and rates are:

1. Cerebral hemorrhage at the time of surgery <1%.
2. Shunt or wound infection <2%.
3. Wound dehiscence <1%.
4. Subdural hygroma 10%.
5. Subdural hematoma 6%.
6. Hematoma or hygroma requiring evacuation 1%.
7. Distal catheter failure 4%.
8. Proximal catheter failure 4%.
9. Valve failure 4%.

**Risk of Delayed Start:** A recent study of the natural history of INPH in which shunt surgery was inadvertently delayed for at least six months for 33 participants in Gothenberg, Sweden, found that without treatment, some participants improved while others worsened before surgery.<sup>14</sup> There is a potential risk of worsening gait and a tendency of falling among participants over the course of the first four months in the placebo group. If a fall is clinically significant, it may result in medical or surgical complications. However, in a recently published open-label randomization study that randomized 93 participants with idiopathic normal pressure hydrocephalus to an immediate vs. postponed treatment group over a similar time period (one year), the proportion of participants with serious adverse events did not differ significantly between the groups.<sup>7</sup>

Additionally, no published experience and little anecdotal experience exist with shunt function following four months in the virtual off setting of >400 mm H<sub>2</sub>O that will be used in the closed shunt group. The potential for increased shunt occlusion after four months of no flow is possible, though less likely with CSF. The risk of CSF leak due to shunt closure is minimal especially in these participants with normal pressure. Other than identifying improvement in outcome measures at four months of active shunting, or identifying significant reduction in ventricular size or other imaging markers consistent with a functioning shunt at four months of active shunting, the only methods to confirm shunt function are radionuclide shunt patency study or, in Europe, CSF infusion testing. These will be performed only as clinically indicated after participants have experienced four months of active shunting.

**Steps Taken to Minimize the Risks:** To minimize overall risks from delay, the accepted time between initial observation and surgical treatment will be limited to six weeks. In addition, this study will collect data on fall frequency, injury and treatment. This data will be reviewed by the clinician and DSMB. Rigorous surgical technique and antisepsis are standard clinical care in shunt implantation. Clinical monitoring for expected complications such as infection are performed so that early intervention may occur. Study participants will be contacted at one and two months post-surgery to ensure their safety. Standard practice recommends the removal of a shunt when determined to be infected.

**Legal Risks:** Every effort will be made to keep the information in the study confidential:

1. Study participants will be assigned a code number and the code number only will be used to identify the clinical/cognitive/biomarker/scanning data;
2. The computers on which the data will be stored are password protected;
3. Written documents concerning the study will be kept in locked areas at the sites.

## 9.4 Benefits

**Direct Benefits:** By taking part of this trial, participants will receive a shunt treatment that might improve their condition and help prevent further deterioration of their health.

**Indirect Benefits:** By being part of the first truly randomized study of shunt surgery in INPH, the participants will help physicians understand the role of surgery in treatment. The findings from this trial would also help in the design of future studies that could determine the degree of improvement in various domains to help prognosticate accurately and the subpopulation that would derive the maximum benefit from shunt surgery.

# 10 Data and Safety Monitoring Plan

## 10.1 Data Safety Monitoring Board (DSMB)

The study will have a DSMB. The DSMB will have a charter, may approve the protocol prior to implementation, and will review interim analyses as applicable. The purpose of the DSMB is to advise the Principal Investigator(s) regarding the continuing safety of study participants and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study participants, adherence to the study protocol, assessments of data quality, performance

of individual clinical center and review of serious adverse events and other safety issues.

The DCC will send reports relating to these topics to DSMB members prior to each DSMB meeting. Interim analyses are anticipated after 10 participants, and then again after approximately two thirds of the target sample size of 40, have been randomized, treated, and have 4-month evaluations available. The DCC will staff the DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by the DSMB Chairperson. These closed minutes will not be available outside the DSMB prior to the end of the study. The DSMB Chairperson will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. When the summary is provided to the DCC, the DCC will send the summary to all clinical center investigators for submission to their respective Institutional Review Boards/Research Ethics Board(s).

## 10.2 Adverse Events Reporting

Assuring participant safety is an essential component of this protocol. Each participating clinical center investigator has primary responsibility for the safety of the individual participants under his or her care. Clinical visits will occur at months 4, 8 and 12 months. Site staff will also call study participants or see them in the clinic at one and two months. Clinical investigators may schedule additional clinic visits according to their standard of care or as needed for clinical reasons. The clinical sites will record all new or worsening symptoms or events as reported by the study participant or documented in the medical records for 30 days after shunt insertion and shunt adjustment. Participating sites will report all neurological, urological and serious adverse events throughout the course of the trial. Other pertinent adverse events can be reported at the discretion of the clinician. All adverse events meeting these definitions occurring after study randomization through final follow up visit will be entered into the electronic data entry system provided by the DCC. In accordance with designated IRB/REB requirements, investigators may be required to report such events to the IRB/REB in addition to notifying the DCC.

### 10.2.1 Definitions, Relatedness, Seriousness and Expectedness

**Definition:** An adverse event (AE) is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom. For purposes of this trial, adverse events that occur from the time of randomization until 12- month follow up visit will be recorded as described above. The principal investigator (PI) at each clinical site will evaluate all adverse events. Adverse events not previously documented in the study will be recorded on the Adverse Event Record Log. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment

should be established.

Falls, however, will be recorded on separate case report forms for the duration of the study and will not be collected on the AE record forms. On the other hand, serious adverse events resulting from falls will be reported as described below in Section 10.2.5.

**Relatedness:** The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the following criteria. *Relatedness may **not** be assessed by a research coordinator, and must be assessed by an investigator.*

**Not Related:** The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, and concomitant drugs or procedures administered to the subject.

**Possibly Related:** The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the study subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

**Probably Related:** The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and cannot reasonably be explained by other factors such as the study subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.

**Seriousness:** The seriousness of clinical adverse events will be recorded by the site investigator and categorized. A serious adverse event (SAE) is an adverse event that:

- results in death; or
- is life-threatening (the participant was, in the view of the clinical site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect); or
- any other event that, based upon appropriate medical judgment, may jeopardize the subjects health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

**Expectedness of the Event:** All adverse events reportable per protocol, including serious adverse events, will be evaluated as to whether their occurrence was expected (as described in the protocol or consent forms) or unexpected.

**Expected:** An event is considered expected if it is known to be associated with the underlying condition (i.e. hydrocephalus) or is related to the study intervention (i.e. shunt placement); and is mentioned in the protocol, informed consent or other study documents. An event may be expected despite the study participant's clinical state immediately prior to the event. For this protocol, expected adverse events include:<sup>6</sup>

1. Subdural hygroma.
2. Subdural hematoma.
3. Hematoma or hygroma requiring evacuation.
4. Epidural hemorrhage.
5. Subarachnoid hemorrhage.
6. Intraventricular hemorrhage.
7. Intraparenchymal hemorrhage.
8. Seizure, acute or chronic.
9. Vascular injury, pseudoaneurysm, dural sinus injury.
10. CSF leak.
11. Bacterial meningitis.
12. Shunt or wound infection.
13. Wound dehiscence.
14. New or increased neurologic deficit.
15. Proximal or distal shunt mis- or displacement.
16. Distal or distal catheter failure.
17. Valve failure.
18. Iatrogenic injury due to shunt passer.

**Unexpected:** An event is considered unexpected if there are no prior data linking this event with either the condition or intervention under study or an event that occurred unexpectedly in the course of surgical treatment.

**Treatment or Action Taken:** For each adverse event, the clinical site will record whether an intervention was required:

- Intervention: Surgery or interventional procedure
- Other Treatment: e.g. medications, therapy, etc.
- Change in shunt setting
- None: No action taken

**Outcome of Event:** Finally, the clinical site will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the participant returned to baseline status
- Recovered with permanent sequelae
- Symptoms continue

### 10.2.2 Time Period for Adverse Events

For purposes of this trial, adverse events will be recorded for 30 days after shunt insertion and shunt adjustment while serious, neurological and urological adverse events will be collected throughout the trial from time of randomization to 12-months follow-up. However, events that occur following participant consent to participate in the trial, but prior to randomization, will not be reported as adverse events. These should be recorded as baseline conditions. If the event has not resolved by the 12-month study visit, the status of the event at this time point should be reported.

### 10.2.3 Data Collection Procedures for Adverse Events

After randomization, adverse events, whether expected or unexpected, will be recorded according to the date of first occurrence, severity, and their duration, as well as any treatment prescribed. Any medical condition that presents prior to randomization will be recorded in the participant's baseline history at study entry but will not be recorded as an adverse event at subsequent evaluations if it remains unchanged. However, worsening of a medical condition that was present at the time prior to randomization will be considered a new adverse event and will be recorded.

Falls will be recorded on a separate case report forms (CRFs). Therefore, they will not be recorded as adverse events.

Abnormal laboratory values that are clinically significant will be recorded as adverse events and the clinical site investigator will assess the severity and relationship to the study. Laboratory values that are abnormal prior to randomization and that do not worsen will not be recorded as adverse events.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding vocabulary. Coding will be done centrally at the DCC because this requires specific training.

#### **10.2.4 Unanticipated Problems (UP)**

Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized.

The site investigator will report unanticipated problems to the DCC within 24 hours. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report these unanticipated problems to the DSMB in an expedited manner (within 24 hours). In accordance with designated IRB/REB requirements, the site investigator may be required to report such unanticipated problems to the IRB/REB in addition to notifying the DCC. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and the DSMB cannot be reached expeditiously, the DCC will notify all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the DSMB.

#### **10.2.5 Monitoring Serious Adverse Events**

A physician from the DCC will act as the medical monitor for this study. If the medical monitor is unavailable, a qualified physician will be designated to fulfill this function. Site investigators and/or research coordinators will report all serious adverse events to the DCC within 24 hours of the event or from the time the investigator became aware of the event. A detailed completed report will be required to be sent to the DCC within 3 working days of the event. After receipt of the complete report, the DCC will report any serious, unexpected, and study-related adverse events to the DSMB in an expedited manner (within 24 hours). In accordance with designated IRB/REB requirements, the clinical site investigator may be required to report such events to the IRB/REB in addition to notifying the DCC. The medical monitor will assess these serious adverse events reported from clinical sites in the trial. For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made. All SAE reports will be retained at the DCC.



In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, the DSMB will be immediately consulted. If the DSMB concurs with the judgment of the medical monitor, or if the DSMB cannot be reached expeditiously, the DCC will notify all site investigators to cease enrollment in the trial and will instruct them to report this to their designated IRB/REB. Resumption of enrollment will not occur without approval of the DSMB. Sites are expected to report serious, unexpected, and study-related SAEs per their designated IRB/REB's expedited reporting requirements. The DSMB will review all adverse events during scheduled DSMB meetings.

#### **10.2.6 Follow-up of Serious, Unexpected and Related Adverse Events**

All serious, unexpected and related adverse events, that are unresolved at the time of the participant's termination from the study or discharge from the hospital, will be followed by the site investigators until the events are resolved, participant is lost to follow-up, the adverse event is otherwise explained or has stabilized, or 12 months have passed from the time of randomization. Adverse experiences that begin after termination from the study will not be recorded as study adverse events.

## **11 Study Training**

A formal training program for investigators and research staff will be held prior to the start of enrollment. The training program will cover regulatory topics and good clinical practice. The training will also provide in depth explanations regarding study procedures, clinical care, adverse event reporting, data entry procedures, quality assurance, site monitoring, and the informed consent process. A manual of operations will be provided to each clinical center investigator prior to the start of enrollment. The manual will detail specific information about the study procedures, regulatory information, safety reporting, and other necessary information. Updates and revisions to the manual will be made available electronically.

## **12 Regulatory Issues**

### **12.1 Health Insurance Portability and Accountability Act (HIPAA)**

Data elements collected include the date of birth and date of admission. Prior to statistical analyses, dates will be used to calculate participant age at the time of the study events. The final data sets (used for study analyses and archived at the end of the study) will be de-identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate participant accrual by race, ethnicity, and gender.

For purposes of the DCC handling potential protected health information (PHI) and producing the de-identified research data sets that will be used for analyses, all study sites have been offered a Business Associate Agreement with the University of Utah. Copies of executed Business Associate Agreements are maintained at the DCC.

## **12.2 Inclusion of Women and Minorities**

There will be no exclusion of participants based on gender, race, or ethnicity.

## **12.3 ClinicalTrials.gov Requirements**

This trial will be registered at ClinicalTrials.gov in accordance with Federal regulations.

## **12.4 Retention of Records**

For federally funded studies subject to the Common Rule, records relating to the research conducted shall be retained for at least three years after completion of the research. These guidelines will be followed for this trial. Completion of the research for this protocol should be anticipated to include planned primary and secondary analyses, as well as subsequent derivative analyses. Completion of the research also entails completion of all publications relating to the research. All records shall be accessible for inspection and copying by authorized representatives of the regulatory authorities at reasonable times and in a reasonable manner [45 CFR x46.115(b)].

## **12.5 Public Use Data Set**

After subject enrollment and follow up have been completed, the DCC will prepare a final study database for analysis. A releasable database will be produced and completely de-identified in accordance with the definitions provided in the Health Insurance Portability and Accountability Act (HIPAA). Namely, all identifiers specified in HIPAA will be recoded in a manner that will make it impossible to deduce or impute the specific identity of any participant. The database will not contain any institutional identifiers.

The DCC will also prepare a data dictionary that provides a concise definition of every data element included in the database. If specific data elements have idiosyncrasies that might affect interpretation or analysis, this will be discussed in the dictionary document. In accordance with policies determined by the investigators and funding sponsors, the releasable database will be provided to users in electronic form.

## 13 Monitoring and Quality Assurance

### 13.1 Tracking Participant Enrollment

Patients that meet all inclusion criteria will be entered into the OpenClinica database. This data, together with the randomization log and the utilization of ICD10 and CPT codes, will allow assessment of numbers of eligible patients, percentage of eligible patients who are approached for consent, and the proportions of eligible/consented participants who are successfully randomized. These results will be regularly reviewed by the DCC or CCC and by the DSMB during scheduled meetings (as described below).

### 13.2 Monitoring and Screening Compliance

As described above, a screening log will be completed for all participants who met the study clinical criteria and were sent for further evaluation, showing final eligibility and ultimate disposition of eligible participants. In addition, it is expected that several of the centers participating in PENS will also participate in the AHCRN Registry, which has been established to track the evaluation of participants seen for adult hydrocephalus. Its goal is to establish a general database of adult hydrocephalus participants to facilitate research in INPH. This Registry has been approved under a separate IRB and is separate from the PENS study.

Assessment of the screening and randomization logs will facilitate assessment of site performance in approaching and assessing participants. At centers participating in the AHCRN Registry, comparison of key characteristics between PENS trial participants and INPH participants enrolled in the registry will further allow an informal assessment of representativeness of PENS trial participants, with respect to key baseline clinical characteristics. While imprecise, such a comparison could detect instances of substantial bias in characteristics of INPH participants recruited into PENS versus others not approached or enrolled.

Protocol compliance will be independently monitored to review the screening data and participant characteristics as described above.

### 13.3 DSMB Evaluation of Screening and Registry Data

An independent DSMB for the PENS trial will evaluate components of the trial, including the screening and participant characteristic data. Study data will be presented to the DSMB on a regular basis, in groupings of certain number of randomizations determined by the enrollment rate, throughout the trial.

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